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DURING MASSIVE γ-IRRADIATION

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A study of the character of lesions occurring during massive irradiation enables us to deepen our concepts of the mechanism of radiation damage and also to note the characteristics of the course of the fulminant form of the disease.

The experiments were carried out on 60 rabbits subjected to whole-body γ-irradiation for 60 min up to a total dose of 30,000 r (dose power 500 r/min). We studied the bioelectrical activity of the brain, the intracranial pressure, circulation rate in the brain vessels, surface temperature of the brain, and also carried out histological investigations of the vessels, nerve fibers, and cells of the brain and glial apparatus. We recorded the time of the occurrence and the characteristics of spasms. We made dynamic observations of the blood pressure, pulse, condition of the peripheral vessels (by the temperature of the ear skin), rectal vessels, change in the electrocardiogram (EKG) and respiration rhythm, composition of the peripheral blood and condition of the hematopoietic organs, and also certain biochemical and general morphological investigations. We killed the animals at the 10th,

30th, and 60th minute of irradiation for the biochemical and morphological investigations.

A special apparatus was developed and used for remote-control complex observations of the animals. The electroencephalograms (EEG), EKG, respiration rhythm, and mechanograms were recorded by an ink-writing device. For recording the EEG we used a multipolar lead—the active electrode was on the parietal region of the cortex, the indifferent electrode was inserted into the bone along the central line at the boundary of the frontal and nasal bones. The respiration rhythm was recorded by a rheostatic pick-up [1] placed on the chest of the rabbit. The spasms were recorded by means of a pendulum-type pick-up mounted on the rabbit's haunch.

The brain, skin, and rectal temperatures were recorded on a photokymograph by means of a specially developed three-channel electrothermometer with an optical recording. The brain thermal pick-up was implanted in a trephined opening in the cranium and brought into contact with the pia mater, the skin temperature pick-up was attached to the rabbit's ear along the path of the central artery. The arterial pressure was measured by the sanguineous method in the femoral artery by means of a U-shaped manometer equipped with an electrical resistance coupled into the scheme of the measuring bridge. The intracranial pressure (VChD) was measured in the rabbit's cisterna cerebellomedullaris where we introduced a needle connected with the water manometer equipped with a photoelectric pressure pick-up. The arterial and intracranial pressures were also recorded on the photokymograph. The volume circulation rate in the brain vessels was recorded in relative units (the scale division of the mirror galvanometer) by the thermoelectric method [10]. A study of the composition of the formed elements of the blood was done by means of an instrument we designed which made it

possible during the experiment to sample by remote-control the rabbit's blood from the carotid artery directly from the circulating stream [2, 7].

Some of these investigations were carried out on the same animal.

During the first 10 min of irradiation, the bioelectrical activity of the brain was enhanced and both the frequency and amplitude of oscillations of the biopotentials increased.

Beginning with the third minute from the start of the effect, the VChD briefly dropped, and simultaneously with this we noted a slowing of the volume blood circulation in the superficial vessels of the brain, which could testify to their stenosis.

Selective damage of the nervous and glial structures was observed at the 10th min of irradiation in the morphologic examination. For instance, in the cerebral cortex, especially in the third stratum, we found sporadic, and here and there small groups of swollen nerve cells among cells with a normal structure. Acute swelling of certain cells was noted in the stratum pyramidale of the hippocampus major and in the brain stems. By this time we noticed scattered foci of demyelination in the conducting system of the brain. Here and there in the white substance of the brain we noted an accumulation of drainage (edematous) forms of oligodendroglia (Nissl's staining method and Dubranskiy's silver-impregnation method), which apparently was a protective reaction to the developing edema of the brain tissue.*

From the very first minutes of irradiation, the number of reticulocytes, thrombocytes, and leukocytes started to drop in the peripheral

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* To avoid errors in evaluating the observed, early morphologic changes in certain structures of the nervous tissue, we simultaneously investigated the morphology of the brain of four unirradiated rabbits kept under the same conditions.

blood, which gradually progressed, and by the end of the exposure their number had dropped an average of 30-50% in comparison with the initial level (Fig. 1). The decline in the number of leukocytes occurred mainly at the expense of granulocytes. We found among these cells degenerative forms, the number of which increased considerably during the course of irradiation. The content of erythrocytes and hemoglobin did not change during irradiation, and at the end of irradiation it increased slightly. We detected among the erythrocytes, hemolyzed forms (shadows) whose number increased in proportion to the exposure. This corresponded to an enhancement of the hemolytic activity of the liver, spleen, and of other organs which was detected in these animals. Erythroblasts, whose number increased and reached 8-10%, appeared in the peripheral blood.

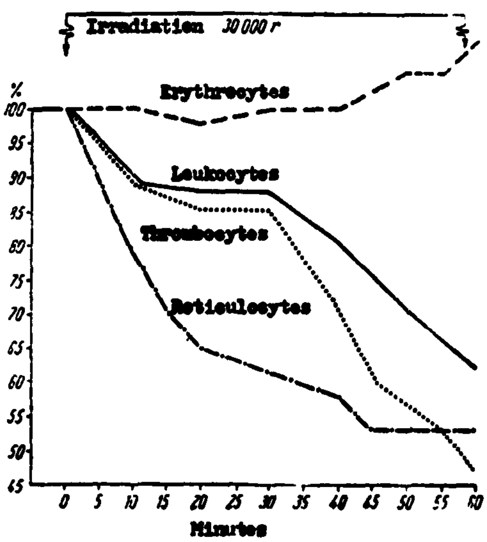

Fig. 1. Number of erythrocytes, reticulocytes, leukocytes, and thrombocytes expressed in per cent of the initial level.

Dividing cells disappeared in the marrow at the 10th minute of irradiation. The number of pyknotic forms of erythroblasts increased

and the proerythroblasts disappeared during irradiation. We at first observed among the myeloid elements an abrupt swelling, disintegration, and dissolution of the nuclear substance, especially in the parental cells (pre- and myelocytes), but later these cells disappeared completely. Hypochromatosis increased in mature granulocytes and cytolysis increased. We detected early damages of the nucleoprotein structure of cells of the myeloid series by luminescent analysis.

The prints of the spleen up to the end of irradiation were rich in blood cells, but the number of lymphocytes decreased with an increase of irradiation, whereas the number of reticuloendothelial cells gradually increased. The number of small pyknotic forms of lymphocytes increased and the lymphoblasts disappeared completely. We observed an increase in the number of reticuloendothelial cells with erythrophagocytosis and with a content of blood pigment which indicated a high intracellular disintegration of erythrocytes. The weight of the spleen did not change during irradiation, however by the end of irradiation the spleen was enlarged, friable, and hyperemized.

Consequently a continuous process of cell necrosis occurred in the hematopoietic organs and in the peripheral blood during irradiation.

The character of the biopotentials of the brain had distinctly changed by the 30th min of irradiation. In some animals the amplitude was increased still more and individual acute waves appeared. Slow rhythms, which later were dominant, were recorded on the EEG of some animals. As a rule these rhythms corresponded to the respiration or pulse rate. At this period the intracranial pressure regularly increased (Fig. 2), the volume rate of blood flow increased in the brain, and edema of the brain tissues grew. Lysis of nerve cells was more evident (Fig. 3). Multiple foci of dissolution of the myelin sheath

appeared, whereas at the 10th min these foci had been sporadic. The development at this stage of a diffuse proliferative reaction of the microglia deserves special attention. However, among the microglial cells (Hortega cells) we observed numerous degenerative forms.

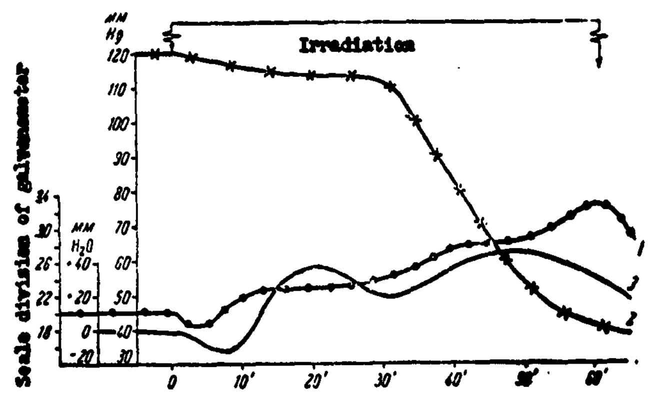

Fig. 2. Change in the intracranial pressure (3), volume rate of blood flow into the brain (1), and the total arterial pressure (2) during γ-irradiation of a rabbit.

During the systematic observation of the condition of the peripheral vessels we could expect that by the 30th min of irradiation they would constrict. The arterial pressure showed a certain tendency to drop.

We observed changes in the EKG: an increase in the PQ interval, of the complex QRS, and splitting of the P-wave.

V. V. Shikhodyrov noted appreciable changes in the myocardial muscle—swelling of the muscle fibers, disappearance of cross striation, vacuolation of the myofibrils. The heart vessels, like the vessels of other organs, underwent similar changes. The arteries were contracted, the veins dilated. A slight edema of the perivascular cellular tissue and capillary hemostasis were noted.

Spastic attacks following one another developed during the last 40-60 min of irradiation. It was established by recording of the mechanograms of 8 rabbits that the spasms occurred between the 40th and 55th minute of irradiation. At first the spasm bore a clonic character, and then became clonicotonic. Brief periods of sharp exaltations followed by a deep depression of the brain biopotentials were recorded during the clonic spasms. The intracranial pressure continued to increase and frequently exceeded the initial level by 30-40 mm H_2O. In a number of experiments, a drop in the intracranial pressure following expressed hypertension was recorded (see Fig. 2). The arterial pressure fell off sharply, the peripheral vessels dilated at this time.

A progressive development of pathologic changes in the brain tissue was morphologically established—edema, especially perivascular and subependymal (third ventricle) was enhanced. A swelling of the walls of certain cells was noted. Changes in the nerve and glial elements bore a dystrophic character with manifestations of focal necrobiosis and necrosis. At this period we observed severe lesion of the neurons of the subthalamic nuclei, in particular the supraoptic nucleus. Widespread degeneration and decomposition were noted from the side of the microglia and oligodendroglia by the end of irradiation (on reaching a dose of 30,000 r), which indicated a suppression of the functions of the glial elements, although the original progressive reaction of the microglia can be considered as a manifestation of its protective properties.

Death of the animals ensued either at the end of irradiation or 30-40 min after the effect of radiation.

The bioelectrical activity sharply dropped in the terminal period. There was a distinct drop of intracranial pressure. The blood supply to the brain diminished. The arterial pressure remained at the former

low level. The peripheral (skin) vessels were dilated. A very appreciable drop in the pulse rate occurred. Group extrasystoles appeared on the EKG, which indicated the development of heterotopic foci of excitation in the heart.

Thus, as early as the first minutes of irradiation we observed a change in the functional condition of the brain. Shifts from the side of the bioelectrical activity of the cerebral cortex were accompanied by a drop of the intracranial pressure and a brief spasm of the brain vessels, which can be explained by the transient increase in the content of free acetylcholine (determined in the brain tissue of these animals). By the 10th minute of irradiation we noted focal morphological changes of the nerve cells and myelin nerve fibers.

Disorders of the functional condition of the nervous system became more pronounced under the effect of further irradiation. This was caused both by the direct damaging action of massive irradiation of the brain, its neurons, and by disturbance of the central-peripheral relationship and interrelationship between the cortex and the subcortical formations. Convincing proof of this is the appearance on the EKG of slow oscillations reflecting the respiration and pulse rhythms. This fact indicates, apparently, facilitated dispersion from the subcortical formations upon weakening of the activity of the cerebral cortex. Considerable importance in disorders of the functional condition of the nervous system is imparted to the afferent impulses from the irradiated receptor zones.

A disorder of the central-peripheral relationship definitely tells on the performance of vegetative functions. For instance, during the simultaneous recording of the bioelectrical activity of the hypothalamus and EKG, we detected a distinct mutual dependence of pathological shifts, which was revealed in the appearance of sharp waves on the

hypothalamogram and an abrupt disturbance of the EKG. The morphological investigations of this period showed profound changes in the hypothalamic nuclei of a dystrophic-necrobiotic nature. Thus, the central nervous system, damaged directly by the ionizing radiation, being subjected, moreover, to enhanced afferent pulsations, is still under unfavorable conditions of blood circulation.

The changes in blood circulation of the brain appeared extremely rapidly.

We tend to think that the original brief decrease in the blood flow is due to regional changes of the brain vessels, their spasm, since the value of the arterial pressure at this time did not change. In spite of certain pathologic shifts on the EEG, the compensatory potentialities of the CNS were not lost, and the brain's blood supply was improved by virtue of the demonstration of protective-adaptive mechanisms. Underlying this adaptive response is the drop of the intracranial pressure which probably occurs as a consequence of deeper respiration, as a result of which the outflow of venous blood and cerebrospinal fluid and the influx of arterial blood are improved.

However, as the dose of irradiation increases, the changes in the CNS increase and the compensatory influences become ever more limited. Respiration becomes frequent and superficial, which affects the intracranial pressure. A drop of arterial pressure causes an even greater dilation of the brain vessels, and the first signs of cerebral edema are demonstrated. All this causes a sharp increase of the intracranial pressure. The expressed ciculatory disorders in the central nervous system, of course, disturb the metabolic processes and thus aggravate the vital activity of the pathologically changed nervous structures.

The "toxic factor" apparently plays a definite role in the developing pathologic process. At present a sufficient amount of data has

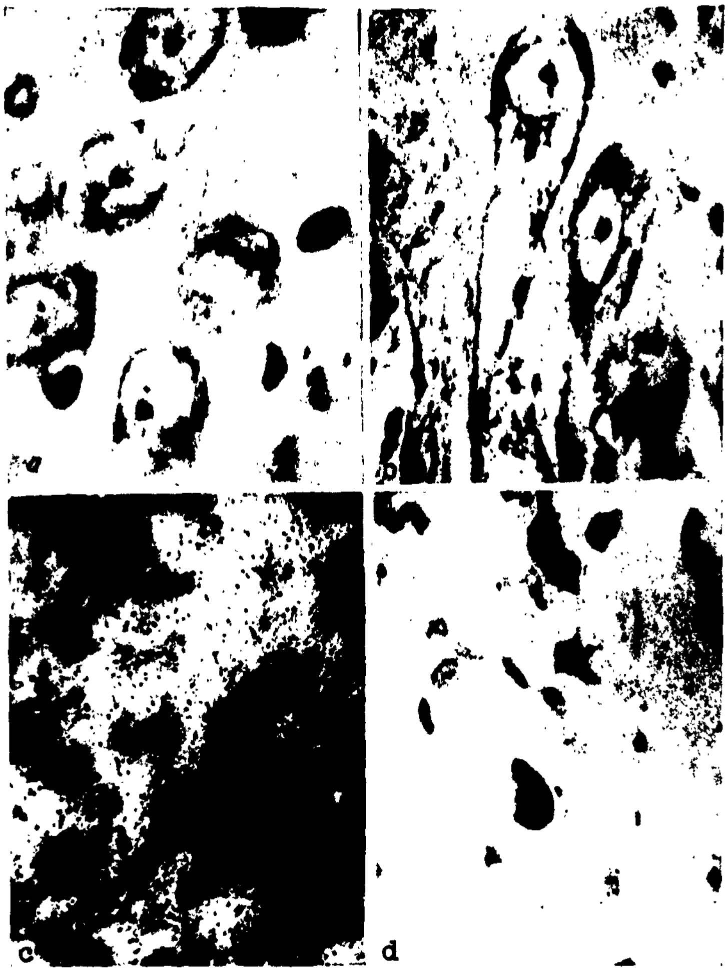

Fig. 3. a) swelling and cytolysis of certain cells of the deep layers of the cerebral cortex in rabbit up to the 30th min of irradiation (dose 150° r); b) edema and evident swelling of cells of the stratum pyramidale hippocampus (dose 1500 r); Nissl's cresyl violet stain. Amplification of immersion X7; c) foci of demyelinization in white subcortical substance. Sokolyanskiy's staining method. Amplification 10 X 10; d) hypothalamus. Wrinkling and karyolysis of nerve cells of rabbit supraoptic nucleus by 60th min of irradiation (dose 30,000 r). Nissl's cresyl violet staining. Amplification 40 X 10.

been accumulated which indicates that biologically active substances can be determined in tissues, blood, and in the lymph upon irradiation [3, 5, 6, 11]. Under our experimental conditions, we noted during the course of irradiation an enhancement of the hemolytic activity of the liver, spleen, kidneys, and muscle tissue, and an increase in the hemolytic activity of the brain tissue was noted for the first time. These data indicate a definite role of toxemia in the development of the fulminant form of radiation sickness.

In regard to the development of spasms, they are preceded as a rule by definite changes in the central nervous system. The recorded, regular slow rhythms indicate a possible synchronous activity of large neuron groups during this period. Such a state of the neurons, in the opinion of M. N. Livanov, fosters generalization of excitation, which is demonstrated as a spastic attack. During the spastic period the morphological changes of the nerve cells of the cortex were more evident, cerebral edema was enhanced even more, and the intracranial pressure increased appreciably. These changes in the dynamics permit us to consider that in severe radiation trauma the spasms are an over-all brain symptom.

In order to elaborate the role of the direct effect of radiation on brain tissue in the development of the spastic syndrome, we set up a series of experiments in which only the brain of some animals was subjected to local γ-irradiation in a dose up to 320,000 r, and the peripheral parts of other rabbits were irradiated (dose power 120 r/a 120 r/sec). On irradiation of the brain the rabbits died, beginning with the 30th min of irradiation or immediately after it. In this case a picture of spasms following one after the other and vestibular disorders with subsequent development of a picture of decerebrate riditity were developed. A series of rapid discharges of great

amplitude, similar to those in general, massive irradiation of the organism, appeared on the EEG during the development period of spastic attacks. After the period of exaltation, a deep depression of the biocurrents developed, and then this cycle of changes was again repeated. On irradiation of the peripheral parts of the body, death of the animals ensued only several days after the effect; there were no spasms in these animals. Therefore, the direct action of radiation on the tissue of the brain plays an essential role in the formation of "radiation spasms."

The terminal period of the fulminant form of radiation sickness occurs against a background of an acute functional emaciation of the cerebral cortex, disorders in the functions of the subjacent divisions of the central nervous system, profound disorders of the blood and cerebrospinal circulation of the brain, and disorders of the entire hemodynamics. Paralysis of the higher centers occurs. Death ensues upon profound morphologic changes, in particular upon severe damage of the nerve cells of the cortex and massive death of the neurons of the hypothalamic nuclei. Consequently there occurs a deep radiation trauma of the organism, and first and foremost, trauma of the nervous system [4, 8, 9].

Conclusions

1. These investigations during the general massive effect of γ-rays on the animal organism have made it possible to reveal very early changes in the central nervous system which are characterized by shifts in the bioelectrical activity of the cerebral cortex, disorders of hemodynamics and cerebrospinal fluid dynamics, and also by lesions of the nerve and glial structures of the brain tissue.

2. The original changes of the brain hemodynamics are not accompanied by noticeable disorders of general hemodynamics. This regionalization of the changes evidently indicates a high radiosensitivity of all structures of the brain, including the vessels. Disorders in the activity of other vitally important systems follow the changes in the CNS.

3. An analysis of the material permits the assertion that the cause of death of the animals in the fulminant form of radiation damage are the severe disorders in the central nervous system.

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